Vaccines and Autism: A Tale of Shifting Hypotheses

Jeffrey S. Gerber and Paul A. Offit
Division of Infectious Diseases, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Although child vaccination rates remain high, some parental concern persists that vaccines might cause autism. Three specific hypotheses have been proposed: (1) the combination measles-mumps-rubella vaccine causes autism by damaging the intestinal lining, which allows the entrance of encephalopathic proteins; (2) thimerosal, an ethylmercury-containing preservative in some vaccines, is toxic to the central nervous system; and (3) the simultaneous administration of multiple vaccines overwhelms or weakens the immune system. We will discuss the genesis of each of these theories and review the relevant epidemiological evidence.

A worldwide increase in the rate of autism diagnoses—likely driven by broadened diagnostic criteria and increased awareness—has fueled concerns that an environmental exposure like vaccines might cause autism. Theories for this putative association have centered on the measles-mumps-rubella (MMR) vaccine, thimerosal, and the large number of vaccines currently administered. However, both epidemiological and biological studies fail to support these claims.

MMR

On 28 February 1998, Andrew Wakefield, a British gastroenterologist, and colleagues [1] published a paper in *The Lancet* that described 8 children whose first symptoms of autism appeared within 1 month after receiving an MMR vaccine. All 8 of these children had gastrointestinal symptoms and signs and lymphoid nodular hyperplasia revealed on endoscopy. From these observations, Wakefield postulated that MMR vaccine caused intestinal inflammation that led to translocation of usually nonpermeable peptides to the bloodstream and, subsequently, to the brain, where they affected development.

Several issues undermine the interpretation by Wakefield et al. [1] of this case series. First, the self-referred cohort did not include control subjects, which precluded the authors from determining whether the occurrence of autism following receipt of MMR vaccine was causal or coincidental. Because ~50,000 British children per month received MMR vaccine between ages 1 and 2 years—at a time when autism typically presents—coincidental associations were inevitable. Indeed, given the prevalence of autism in England in 1998 of 1 in 2000 children [2], ~25 children per month would receive a diagnosis of the disorder soon after receiving MMR vaccine by chance alone. Second, endoscopic or neuropsychological assessments were not blind, and data were not collected systematically or completely. Third, gastrointestinal symptoms did not predate autism in several children, which is inconsistent with the notion that intestinal inflammation facilitated bloodstream invasion of encephalopathic peptides. Fourth, measles, mumps, or rubella vaccine viruses have not been found to cause chronic intestinal inflammation or loss of intestinal barrier function. Indeed, a recent study by Hornig et al. [3] found that the measles vaccine virus genome was not detected more commonly in children with or without autism. Fifth, putative encephalopathic peptides traveling from the intestine to the brain have never been identified. In contrast, the genes that have been associated with autism spectrum disorder to date have been found to code for endogenous proteins that influence neuronal synapse function, neuronal cell adhesion, neuronal activity regulation, or endosomal trafficking [4].

Although no data supporting an association between MMR vaccine and autism existed and a plausible biological mechanism was lacking, several epidemiologic studies were performed to address parental fears created by the publication by Wakefield et al. [1] (table 1). Fortunately, several features of large-scale vaccination programs allowed for excellent descriptive and observational studies—specifically, large numbers of subjects, which generated substantial statistical power; high-quality vac-

Received 25 August 2008; accepted 14 October 2008; electronically published 7 January 2009.

Reprints or correspondence: Dr. Paul A. Offit, Div. of Infectious Diseases, The Children's Hospital of Philadelphia, Abramson Research Center, Rm. 1202, 3561 Civic Center Blvd., Philadelphia, PA 19104-4399 (offit@email.chop.edu).

Clinical Infectious Diseases 2009; 48:456–61

1058-4838/2009/4804-0015$15.00
DOI: 10.1086/596476

Table 1. Studies that fail to support an association between measles-mumps-rubella vaccine and autism.

Source	Study design	Study location
Taylor et al., 1999 [5]	Ecological	United Kingdom
Farrington et al., 2001 [6]	Ecological	United Kingdom
Kaye et al., 2001 [7]	Ecological	United Kingdom
Dales et al., 2001 [8]	Ecological	United States
Fombonne et al., 2006 [9]	Ecological	Canada
Fombonne and Chakrabarti, 2001 [10]	Ecological	United Kingdom
Taylor et al., 2002 [11]	Ecological	United Kingdom
DeWilde et al., 2001 [12]	Case-control	United Kingdom
Makela et al., 2002 [13]	Retrospective cohort	Finland
Madsen et al., 2002 [14]	Retrospective cohort	Denmark
DeStefano et al., 2004 [15]	Case-control	United States
Peltola et al., 1998 [16]	Prospective cohort	Finland
Patja et al., 2000 [17]	Prospective cohort	Finland

cination records, which provided reliable historical data; multinational use of similar vaccine constituents and schedules; electronic medical records, which facilitated accurate analysis of outcome data; and the relatively recent introduction of MMR vaccine in some countries, which allowed for before and after comparisons.

Ecological studies. Researchers in several countries performed ecological studies that addressed the question of whether MMR vaccine causes autism. Such analyses employ large databases that compare vaccination rates with autism diagnoses at the population level.

1. In the United Kingdom, researchers evaluated 498 autistic children born from 1979 through 1992 who were identified by computerized health records from 8 health districts [5]. Although a trend toward increasing autism diagnoses by year of birth was confirmed, no change in the rates of autism diagnoses after the 1987 introduction of MMR vaccine was observed. Further, MMR vaccination rates of autistic children were similar to those of the entire study population. Also, investigators did not observe a clustering of autism diagnoses relative to the time that children received MMR vaccine, nor did they observe a difference in age at autism diagnosis between those vaccinated and not vaccinated or between those vaccinated before or after 18 months of age. These authors also found no differences in autism rates among vaccinated and unvaccinated children when they extended their analysis to include a longer time after MMR exposure or a second dose of MMR [6].
2. Also in the United Kingdom, researchers performed a time-trend analysis using the General Practice Research Database—a high-quality, extensively validated electronic medical record with virtually complete vaccination data [7]. More than 3 million person-years of observation during 1988–1999 confirmed an increase in autism diagnoses despite stable MMR vaccination rates.
3. In California, researchers compared year-specific MMR vaccination rates of kindergarten students with the yearly autism case load of the California Department of Developmental Services during 1980–1994 [8]. As was observed in the United Kingdom, the increase in the number of autism diagnoses did not correlate with MMR vaccination rates.
4. In Canada, researchers estimated the prevalence of pervasive developmental disorder with respect to MMR vaccination in 27,749 children from 55 schools in Quebec [9]. Autism rates increased coincident with a decrease in MMR vaccination rates. The results were unchanged when both exposure and outcome definitions varied, including a strict diagnosis of autism.

Additional population-based studies considered the relationship between MMR vaccine and the "new variant" form of autism proposed by Wakefield et al. [1]—specifically, developmental regression with gastrointestinal symptoms. Although it is difficult to analyze such a phenomenon when it is unclear that one exists (which complicates the formulation of a case definition), conclusions may be gleaned from the data with respect to developmental regression alone (i.e., autism irrespective of coincident bowel problems).

1. In England, researchers performed a cross-sectional study of 262 autistic children and demonstrated no difference in age of first parental concerns or rate of developmental regression by exposure to MMR vaccine [10]. No association between developmental regression and gastrointestinal symptoms was observed.
2. In London, an analysis of 473 autistic children used the 1987 introduction of MMR to compare vaccinated and

unvaccinated cohorts [11]. The incidence of developmental regression did not differ between cohorts, and the authors observed no difference in the prevalence of gastrointestinal symptoms between vaccinated and unvaccinated autistic children.

Two conclusions are evident from these data. First, the explicit consideration of developmental regression among autistic children does not alter the consistent independence of MMR vaccine and autism. Second, these data argue against the existence of a new variant form of autism.

Retrospective, observational studies. Four retrospective, observational studies addressed the relationship between MMR vaccine and autism.

1. In the United Kingdom, 71 MMR-vaccinated autistic children were compared with 284 MMR-vaccinated matched control children through use of the Doctor's Independent Network, a general practice database [12]. The authors observed no differences between case and control children in practitioner consultation rates—a surrogate for parental concerns about their child's development—within 6 months after MMR vaccination, which suggests that the diagnosis of autism was not temporally related to MMR vaccination.
2. In Finland, using national registers, researchers linked hospitalization records to vaccination records in 535,544 children vaccinated during 1982–1986 [13]. Of 309 children hospitalized for autistic disorders, no clustering occurred relative to the time of MMR vaccination.
3. In Denmark, again using a national registry, researchers determined vaccination status and autism diagnosis in 537,303 children born during 1991–1998 [14]. The authors observed no differences in the relative risk of autism between those who did and those who did not receive MMR vaccine. Among autistic children, no relationship between date of vaccination and development of autism was observed.
4. In metropolitan Atlanta, using a developmental surveillance program, researchers compared 624 autistic children with 1824 matched control children [15]. Vaccination records were obtained from state immunization forms. The authors observed no differences in age at vaccination between autistic and nonautistic children, which suggests that early age of MMR vaccine exposure was not a risk factor for autism.

Prospective observational studies. Capitalizing on a long-term vaccination project maintained by the National Board of Health, investigators in Finland performed 2 prospective cohort studies. Researchers prospectively recorded adverse events associated with MMR-vaccinated children during 1982–1996 and identified 31 with gastrointestinal symptoms; none of the children developed autism [16]. A further analysis of this cohort revealed no vaccine-associated cases of autism among 1.8 million children [17]. Although this cohort was analyzed using a passive surveillance system, the complete absence of an association between gastrointestinal disease and autism after MMR vaccination was compelling.

THIMEROSAL

Thimerosal—50% ethylmercury by weight—is an antibacterial compound that has been used effectively in multidose vaccine preparations for >50 years [18] (thimerosal is not contained in live-virus vaccines, such as MMR). In 1997, the US Food and Drug Administration Modernization Act mandated identification and quantification of mercury in all food and drugs; 2 years later, the US Food and Drug Administration found that children might be receiving as much as 187.5 μg of mercury within the first 6 months of life. Despite the absence of data suggesting harm from quantities of ethylmercury contained in vaccines, in 1999, the American Academy of Pediatrics and the Public Health Service recommended the immediate removal of mercury from all vaccines given to young infants [19]. Widespread and predictable misinterpretation of this conservative, precautionary directive, coupled with a public already concerned by a proposed but unsubstantiated link between vaccination and autism, understandably provoked concern among parents, which led to the birth of several antimercury advocacy groups. However, because the signs and symptoms of autism are clearly distinct from those of mercury poisoning, concerns about mercury as a cause of autism were—similar to those with MMR vaccine—biologically implausible [20]; children with mercury poisoning show characteristic motor, speech, sensory, psychiatric, visual, and head circumference changes that are either fundamentally different from those of or absent in children with autism. Consistent with this, a study performed by scientists at the Centers for Disease Control and Prevention years later showed that mercury in vaccines did not cause even subtle signs or symptoms of mercury poisoning [21].

Despite the biological implausibility of the contention that thimerosal in vaccines caused autism, 7 studies—again descriptive or observational—were performed (table 2). Four other

Table 2. Studies that fail to support an association between thimerosal in vaccines and autism.

Source	Study design	Location
Stehr-Green et al., 2003 [22]	Ecological	Sweden and Denmark
Madsen et al., 2003 [23]	Ecological	Denmark
Fombonne et al., 2006 [9]	Ecological	Canada
Hviid et al., 2003 [24]	Retrospective cohort	Denmark
Verstraeten et al., 2003 [25]	Retrospective cohort	United States
Heron and Golding, 2004 [26]	Prospective cohort	United Kingdom
Andrews et al., 2004 [27]	Retrospective cohort	United Kingdom

studies have been reviewed in detail elsewhere [28] but are not discussed here because their methodology is incomplete and unclear and, thus, cause difficulty in drawing meaningful conclusions.

Ecological studies. Three ecological studies performed in 3 different countries compared the incidence of autism with thimerosal exposure from vaccines. In each case, the nationwide removal of thimerosal—which occurred in 1992 in Europe and in 2001 in the United States—allowed robust comparisons of vaccination with thimerosal-containing and thimerosal-free products, as follows:

1. In Sweden and Denmark, researchers found a relatively stable incidence of autism when thimerosal-containing vaccines were in use (1980–1990), including years when children were exposed to as much as 200 μg of ethylmercury (concentrations similar to peak US exposures) [22]. However, in 1990, a steady increase in the incidence of autism began in both countries and continued through the end of the study period in 2000, despite the removal of thimerosal from vaccines in 1992.
2. In Denmark, researchers performed a study comparing the incidence of autism in children who had received 200 μg (1961–1970), 125 μg (1970–1992), or 0 μg of thimerosal (1992–2000) and again demonstrated no relationship between thimerosal exposure and autism [23].
3. In Quebec, researchers grouped 27,749 children from 55 schools by date of birth and estimated thimerosal exposure on the basis of the corresponding Ministry of Health vaccine schedules. School records were obtained to determine age-specific rates of pervasive developmental disorder [9]. Thimerosal exposure and pervasive developmental disorder diagnosis were found to be independent variables. Similar to previous analyses, the highest rates of pervasive developmental disorder were found in cohorts exposed to thimerosal-free vaccines. The results were unchanged when both exposure and outcome definitions varied.

Cohort studies. Four cohort studies that examined thimerosal exposure and autism have been performed, as follows:

1. In Denmark, researchers examined >1200 children with autism that was identified during 1990–1996, which comprised ~3 million person-years. They found that the risk of autism did not differ between children vaccinated with thimerosal-containing vaccines and those vaccinated with thimerosal-free vaccines or between children who received greater or lower quantities of thimerosal [24]. They also found that the rates of autism increased after the removal of thimerosal from all vaccines.
2. In the United States, using the Vaccine Safety Data Link, researchers at the Centers for Disease Control and Prevention examined 140,887 US children born during 1991–1999, including >200 children with autism [25]. The researchers found no relationship between receipt of thimerosal-containing vaccines and autism.
3. In England, researchers prospectively followed 12,810 children for whom they had complete vaccination records who were born during 1991–1992, and they found no relationship between early thimerosal exposure and deleterious neurological or psychological outcomes [26].
4. In the United Kingdom, researchers evaluated the vaccination records of 100,572 children born during 1988–1997, using the General Practice Research Database, 104 of whom were affected with autism [27]. No relationship between thimerosal exposure and autism diagnosis was observed.

TOO MANY VACCINES

When studies of MMR vaccine and thimerosal-containing vaccines failed to show an association with autism, alternative theories emerged. The most prominent theory suggests that the simultaneous administration of multiple vaccines overwhelms or weakens the immune system and creates an interaction with the nervous system that triggers autism in a susceptible host. This theory was recently popularized in the wake of a concession by the Vaccine Injury Compensation Program with regard to the case of a 9-year-old girl with a mitochondrial enzyme deficiency whose encephalopathy, which included features of autism spectrum disorder, was judged to have worsened following the receipt of multiple vaccines at age 19 months [29]. Despite reassurances by the Centers for Disease Control and Prevention that the Vaccine Injury Compensation Program's action should not be interpreted as scientific evidence that vaccines cause autism, many in the lay press and the public have not been reassured.

The notion that children might be receiving too many vaccines too soon and that these vaccines either overwhelm an immature immune system or generate a pathologic, autism-inducing autoimmune response is flawed for several reasons:

1. Vaccines do not overwhelm the immune system. Although the infant immune system is relatively naive, it is immediately capable of generating a vast array of protective responses; even conservative estimates predict the capacity to respond to thousands of vaccines simultaneously [30]. Consistent with this theoretical exercise, combinations of vaccines induce immune responses comparable to those given individually [31]. Also, although the number of recommended childhood vaccines has increased during the past 30 years, with advances in protein chemistry and recombinant DNA technology, the immunologic load has actually decreased. The 14 vaccines given today contain

<200 bacterial and viral proteins or polysaccharides, compared with >3000 of these immunological components in the 7 vaccines administered in 1980 [30]. Further, vaccines represent a minute fraction of what a child's immune system routinely navigates; the average child is infected with 4–6 viruses per year [32]. The immune response elicited from the vast antigen exposure of unattenuated viral replication supersedes that of even multiple, simultaneous vaccines.

2. Multiple vaccinations do not weaken the immune system. Vaccinated and unvaccinated children do not differ in their susceptibility to infections not prevented by vaccines [33–35]. In other words, vaccination does not suppress the immune system in a clinically relevant manner. However, infections with some vaccine-preventable diseases predispose children to severe, invasive infections with other pathogens [36, 37]. Therefore, the available data suggest that vaccines do not weaken the immune system.
3. Autism is not an immune-mediated disease. Unlike autoimmune diseases such as multiple sclerosis, there is no evidence of immune activation or inflammatory lesions in the CNS of people with autism [38]. In fact, current data suggest that genetic variation in neuronal circuitry that affects synaptic development might in part account for autistic behavior [39]. Thus, speculation that an exaggerated or inappropriate immune response to vaccination precipitates autism is at variance with current scientific data that address the pathogenesis of autism.
4. No studies have compared the incidence of autism in vaccinated, unvaccinated, or alternatively vaccinated children (i.e., schedules that spread out vaccines, avoid combination vaccines, or include only select vaccines). These studies would be difficult to perform because of the likely differences among these 3 groups in health care seeking behavior and the ethics of experimentally studying children who have not received vaccines.

CONCLUSIONS

Twenty epidemiologic studies have shown that neither thimerosal nor MMR vaccine causes autism. These studies have been performed in several countries by many different investigators who have employed a multitude of epidemiologic and statistical methods. The large size of the studied populations has afforded a level of statistical power sufficient to detect even rare associations. These studies, in concert with the biological implausibility that vaccines overwhelm a child's immune system, have effectively dismissed the notion that vaccines cause autism. Further studies on the cause or causes of autism should focus on more-promising leads.

Acknowledgments

Potential conflicts of interest. P.A.O. is a coinventor and patent coholder of the rotavirus vaccine Rotateq and has served on a scientific advisory board to Merck. J.S.G.: no conflicts.

References

1. Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet **1998**; 351:637–41.
2. Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? Lancet **1998**; 351:611–2.
3. Hornig M, Briese T, Buie T, et al. Lack of association between measles virus vaccine and autism with enteropathy: a case-control study. PLoS ONE **2008**; 3:e3140.
4. Sutcliffe JS. Genetics: insights into the pathogenesis of autism. Science **2008**; 321:208–9.
5. Taylor B, Miller E, Farrington CP, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet **1999**; 353:2026–9.
6. Farrington CP, Miller E, Taylor B. MMR and autism: further evidence against a causal association. Vaccine **2001**; 19:3632–5.
7. Kaye JA, del Mar Melero-Montes M, Jick H. Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. BMJ **2001**; 322:460–3.
8. Dales L, Hammer SJ, Smith NJ. Time trends in autism and in MMR immunization coverage in California. JAMA **2001**; 285:1183–5.
9. Fombonne E, Zakarian R, Bennett A, Meng L, McLean-Heywood D. Pervasive developmental disorders in Montreal, Quebec, Canada: prevalence and links with immunizations. Pediatrics **2006**; 118:e139–50.
10. Fombonne E, Chakrabarti S. No evidence for a new variant of measles-mumps-rubella–induced autism. Pediatrics **2001**; 108:e58.
11. Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J. Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study. BMJ **2002**; 324: 393–6.
12. DeWilde S, Carey IM, Richards N, Hilton SR, Cook DG. Do children who become autistic consult more often after MMR vaccination? Br J Gen Pract **2001**; 51:226–7.
13. Makela A, Nuorti JP, Peltola H. Neurologic disorders after measles-mumps-rubella vaccination. Pediatrics **2002**; 110:957–63.
14. Madsen KM, Hviid A, Vestergaard M, et al. A population-based study of measles, mumps, and rubella vaccination and autism. N Engl J Med **2002**; 347:1477–82.
15. DeStefano F, Bhasin TK, Thompson WW, Yeargin-Allsopp M, Boyle C. Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta. Pediatrics **2004**; 113:259–66.
16. Peltola H, Patja A, Leinikki P, Valle M, Davidkin I, Paunio M. No evidence for measles, mumps, and rubella vaccine–associated inflammatory bowel disease or autism in a 14-year prospective study. Lancet **1998**; 351:1327–8.
17. Patja A, Davidkin I, Kurki T, Kallio MJ, Valle M, Peltola H. Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up. Pediatr Infect Dis J **2000**; 19:1127–34.
18. Baker JP. Mercury, vaccines, and autism: one controversy, three histories. Am J Public Health 2008; 98:244–53.
19. Centers for Disease Control and Prevention. Thimerosal in vaccines: a joint statement of the American Academy of Pediatrics and the Public Health Service. MMWR Morb Mortal Wkly Rep **1999**; 48:563–5.
20. Nelson KB, Bauman ML. Thimerosal and autism? Pediatrics **2003**; 111: 674–9.
21. Thompson WW, Price C, Goodson B, et al. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. N Engl J Med **2007**; 357:1281–92.
22. Stehr-Green P, Tull P, Stellfeld M, Mortenson PB, Simpson D. Autism

and thimerosal-containing vaccines: lack of consistent evidence for an association. Am J Prev Med **2003**; 25:101–6.
23. Madsen KM, Lauritsen MB, Pedersen CB, et al. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. Pediatrics **2003**; 112:604–6.
24. Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerosal-containing vaccine and autism. JAMA **2003**; 290:1763–6.
25. Verstraeten T, Davis RL, DeStefano F, et al. Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. Pediatrics **2003**; 112:1039–48.
26. Heron J, Golding J. Thimerosal exposure in infants and developmental disorders: a prospective cohort study in the United Kingdom does not support a causal association. Pediatrics **2004**; 114:577–83.
27. Andrews N, Miller E, Grant A, Stowe J, Osborne V, Taylor B. Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United Kingdom does not support a causal association. Pediatrics **2004**; 114:584–91.
28. Parker SK, Schwartz B, Todd J, Pickering LK. Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data. Pediatrics **2004**;114:793–804.
29. Offit PA. Vaccines and autism revisited—the Hannah Poling case. N Engl J Med **2008**; 358:2089–91.
30. Offit PA, Quarles J, Gerber MA, et al. Addressing parents' concerns: do multiple vaccines overwhelm or weaken the infant's immune system? Pediatrics **2002**; 109:124–9.
31. King GE, Hadler SC. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. Pediatr Infect Dis J **1994**; 13:394–407.
32. Dingle JH, Badger GF, Jordan WS Jr. Illness in the home: a study of 25,000 illnesses in a group of Cleveland families. Cleveland: Press of Western Reserve University, **1964**.
33. Black SB, Cherry JD, Shinefield HR, Fireman B, Christenson P, Lampert D. Apparent decreased risk of invasive bacterial disease after heterologous childhood immunization. Am J Dis Child **1991**; 145:746–9.
34. Davidson M, Letson GW, Ward JI, et al. DTP immunization and susceptibility to infectious diseases: is there a relationship? Am J Dis Child **1991**; 145:750–4.
35. Storsaeter J, Olin P, Renemar B, et al. Mortality and morbidity from invasive bacterial infections during a clinical trial of acellular pertussis vaccines in Sweden. Pediatr Infect Dis J **1988**; 7:637–45.
36. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. Clin Infect Dis **2000**; 30:784–9.
37. Laupland KB, Davies HD, Low DE, Schwartz B, Green K, McGeer A. Invasive group A streptococcal disease in children and association with varicella-zoster virus infection. Ontario Group A Streptococcal Study Group. Pediatrics **2000**; 105:e60.
38. McCormick MC. Immunization safety review: vaccines and autism. Washington, DC: Institute of Medicine, **2004**.
39. Morrow EM, Yoo SY, Flavell SW, et al. Identifying autism loci and genes by tracing recent shared ancestry. Science **2008**; 321:218–23.